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(54) CONTROLLED RELEASE OF DRUGS DELIVERED BY SUBLINGUAL OR BUCCAL ADMINISTRATION

GESTEUERTE FREISETZUNG VON SUBLINGUAL ODER BUKKAL VERABREICHTEN ARZNEISTOFFEN

MEDICAMENTS A LIBERATION CONTROLEE ADMINISTRES PAR VOIE SUBLINGUALE OU BUCCALE

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(56) References cited:
WO-A-96/41619
WO-A-97/06786
US-A- 5 770 606

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Description

Field of the Invention

[0001] This invention relates to a composition for the controlled release of apomorphine HCl for administration via either sublingual or buccal route and suitable for treating erectile dysfunction.

Background of the Invention

[0002] The term "impotence" has been used to signify the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse. The term "erectile dysfunction" has been suggested as a more precise term "to signify an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function." Droller, M.J. et al. Impotence. Consensus Development Conference Statement, National Institutes of Health (1993).

[0003] Erectile disfunction may result from psychological causes (psychogenic erectile dysfunction) or organic causes or a combination. Organic causes include physiological, nervous, vascular and hormonal pathologies or a combination thereof.

[0004] The normal physiology of an erection involves nerve impulses which signal certain muscles to relax. These muscles, when contracted, restrict blood flow through arteries in the penis. When relaxed, the muscles permit a significant increase in blood flow. The increased blood flow engorges three groups of erectile tissue within the penis with blood and the penis becomes less flaccid. The engorged erectile tissue and the muscle structure of the penis depress adjacent veins, restricting the flow of blood out of the penis. The restriction of blood flow out of the penis increases and sustains the erection.

[0005] Deficiencies of some hormones, such as testosterone, or elevation of others, such as prolactin, can cause erectile dysfunction. Many drugs, such diuretics, antihypertensives, anticonvulsants, narcotics, alcohol, and psychotropic drugs may cause erectile disfunction as a side effect. Murray, F.T. et al. *Amer. J. Medical Sci.* **309**: 99-109 (1995).

[0006] Damage to nerves and blood vessels may also provide an organic cause for erectile dysfunction. Disease processes may involve several aspects. For example, diabetes, which causes damage to both nerves and blood vessels, can cause erectile dysfunction. A significant percent of all diabetic men will suffer from erectile dysfunction.

[0007] Methods proposed for the treatment of erectile dysfunction have included external devices, sex therapy, surgical implantation of internal prostheses, injection of drugs directly into the penis and topically applied medications. None of these approaches is entirely effective.

[0008] External devices include tourniquets (see U.S. Patent No 2,818,855) and externally applied vacuum erection aids. While some clinicians consider externally applied erection aids as a first option for treatment, some patients are unwilling to use such devices. O'Keefe, M., et al. *Medical Clinics of North America* 79: 415-434 (1995).

[0009] Symptomatic sex therapy was originally found to be effective by Masters and Johnson, but later studies have not shown as impressive results. Freudian therapy does not appear to patients to be an attractive alternative. Vickers, M.A., et al. *J. Urology* **149**: 1258-1261 (1993).

[0010] Surgically implanted mechanical devices, such as hinged or solid rods and inflatable, spring driven or hydraulic prostheses have been used for some time.

[0011] The administration of erection effecting and enhancing drugs is taught in U.S. Patent No. 4,127,118 to LaTorre. This patent teaches a method of treating male impotence by injecting into the penis an appropriate vasodilator, in particular, an adrenergic blocking agent or a smooth muscle relaxant to effect and enhance an erection.

[0012] More recently, U.S. Patent No. 4,801587 to Voss et al. teaches the application of an ointment to relieve impotence. The ointment consists of the vasodilators papaverine, hydralazine, sodium nitroprusside, phenoxybenzamine, or phentolamine and a carrier to assist absorption of the primary agent through the skin. U.S. Patent No. 5,256,652 to El-Rashidy teaches the use of an aqueous topical composition of a vasodilator such as papaverine together with hydroxypropyl-β-cyclodextrin.

[0013] Recently the effect of apomorphine on penile tumescence in male patients afflicted with psychogenic impotence has been studied. Segraves, R,T, et. al. *J. Urology* **145**: 1174-1175 (1991). These studies show that while apomorphine can indeed induce an erection in a psychogenic male patient, the apomorphine dose required to achieve a significant erectile response is usually accompanied by nausea or other serious undesirable side effects such as hypertension, flushing and diaphoresis.

[0014] Studies measuring the bioavailability, the bioavailable dose, the rate of absorption, elimination, and metabolism for apomorphine have been reported. Muhtadi, F.J. and M.S. Hifnawy, Analytical Profile of Apomorphine Hydrochloride, in Analytical Profiles of Drug Substances, Klaus Florely Ed., Vol 20, Academic Press, Inc. New York (1991). Traditional routes of . administration, such as oral tablet and liquid preparations have been shown to be relatively ineffective in establishing a blood plasma level for this drug compared to parenteral administration. However, the sub-

lingual route of administration has been investigated for the treatment of Parkinson's disease. In that study, sublingual apomorphine was found to be about 10% bioavailable compared to parenteral administration. Deffond, D, et al. *J. Neurol. Neurosurg. and Psych.* 56:101-103 (1993).

[0015] WO 97/06786 discloses a pharmaceutical composition for oral administration comprising a dopamine agonist as active ingredient, characterized in that the composition is in the form of a fast-dispersing dosage form designed rapidly to release the active ingredient in the oral cavity and the use of such composition for the treatment and/or evaluation of Parkinson's disease.

[0016] Sublingual tablets are well documented in the literature since the beginning of this century. The main reason for sublingual route of drug administration is to provide a rapid onset of action of potent drugs. Another reason is to avoid the first pass metabolism by the liver. The term "controlled release" when applied to sublingual tablets is limited to a maximum of about 60 minutes. Traditional sublingual tablets are usually designed as water soluble tablets made of water soluble sugars such as sorbitol, lactose, mannitol, etc. In the literature, controlled release sublingual tablets are very scarce.

[0017] Time release sublingual medications are disclosed in U.S. Pat. No. 3,428,728 issued to Lowey. (1969), perhaps due to the limited residence time in the sublingual cavity, or poor patient compliance, or acceptance of having a foreign body under the tongue for extended periods of time.

[0018] Lowey described a controlled release sublingual tablet made by cooking gum acacia and sorbitol (by heating) till partial dryness followed by addition of citric acid, color and flavor followed by cooling. Active ingredients such as nitroglycerin, caffeine, guaiocolate, amylase or isoproterenol were then added to the pourable paste that was cast into tablets. However, Lowey's discovery cannot be applied to make tablets by compression.

[0019] WO 96/41619 discloses a composition providing a relatively slow release of water-soluble drugs, such as apomorphine, for delivery via the sublingual or buccal routes. In particular, this document discloses a composition consisting essentially of about 2 to about 10 mg of a water-solubie drug, an osmotic agent, a swellable hydrophilic carrier, and a water dispersable polymer, wherein the composition has a T_{90} value in the range of more than about 25 to about 300.

[0020] The time of release for a pharmaceutical preparation is critical to the effectiveness of the drug. An immediate release of the drug such as a solution of apomorphine placed under the tongue results in an overwhelming percentage of undesirable side effects. Heaton, J.P.W. et al. Recovery of erectile function by the oral administration of apomorphine *Urology* 45: 200-206 (1995). The sublingual tablets of the present invention provide a relatively slow controlled apomorphine HCl release as compared with a conventional soluble tablet, and thus dramatically reduce the undesirable side effects of apomorphine.

[0021] What is needed is an effective treatment of psychogenic erectile dysfunction that involves minimal mechanical distractions and unwanted side effects.

Summary of the Invention

[0022] The present invention provides apomorphine direct compression tablets suitable for sublingual or buccal administration, having a drug release time T_{90} value in the range of 30 to 45 minutes and suitable for treating psychogenic erectile dysfunction, comprising the following components (mg/tablet) and wherein each component passes through a 30 mesh screen in either composition R or composition S:

	Composition	
Ingradient (mg/tablet)	R	S
Apomorphine HCl USP	40.0	40.0
Ascorbic Acid, USP	7.5	8.4
Citric Acid, Anhydrous, NF	5.0	5.6
Microcrystalline Cellulose, NF (Avical PH102)	57.0	39.3
Magnesium Stearate, NF	3.0	2.8
Hydroxypropyl methylcellulose (Methocel E4M Premium, NF)	12.5	8.4
Turquoise Lake	3.0	2.8
Aspartame, USP	2.5	2.8
Mannitol, USP, powder	19.5	30.0
TOTAL, mg/tablet	150.0	140.0

The tablets of the invention permit apomorphine HCl to achieve its effective therapeutic plasma concentration which

is below a plasma concentration where undesirable side effects such as nausea and vomiting occur. In addition to this major improvement arising from the present invention, the added benefit or apomorphine HCl release over a longer period of time from the tablet can increase the duration of the therapeutic activity for apomorphine HCl.

[0023] The tablets of the invention deliver apomorphine HCl at a controlled rate to produce the desired physiological effect of apomorphine HCl while preventing or diminishing the side effects such as hypotension, nausea and vomiting that have been associated with apomorphine. The tablets of the invention thus provide the therapeutic benefits of apomorphine, as for example, in the treatment of Male Erectile Dysfunction with minimal side effects.

Brief Description of the Drawings

[0024] In the drawings,

FIGURE 1 is a graph of the dissolution of the direct compression apomorphine compositions of Examples 2 and 3.

Detailed Description of Preferred Embodiments

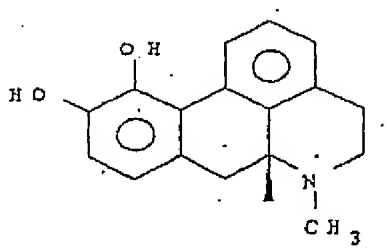
[0025] The present invention provides controlled release tablets suitable for sublingual or buccal delivery of apomorphine HCl. For the tablets of the invention , 90 percent by weight of the apomorphine present is released in a water solution over a time period in the range of 30 minutes to 45 minutes. In the ensuing specification and claims, the release time is referred to as a T_{90} value. That is, the present compositions have a T_{90} value in the range of 30 minutes to 45 minutes.

[0026] The tablets of the invintion comprise microcrystalline cellulose as water-insoluble carrier whose porous structure is filled, coated, or covered by apomorphine HCl; and mannitol as osmotic agent. The above drug-loaded carrier system is mixed with hydroxypropyl methylcellulose as water dispersible polymer and subjected to direct compression into a tablet. Upon contact of the tablets of this invention with biological fluids, such as saliva, and with the aid of the osmotic agent, two opposing phenomena occur simultaneously.

1. Gelling of the hydroxypropyl methylcellulose which slows the drug diffusion from the tablet matrix.
2. Swelling of the microcrystalline cellulose providing more surface area for further fluid penetration with aqueous channel formation, leading to a faster diffusion or release of the active ingredient.

[0027] The treatment of psychogenic impotence can be achieved by the administration of the apomorphine tablets of the invention preferably about 15 to about 45 minutes prior to sexual activity.

[0028] Apomorphine can be represented by the formula:



and exists in a free base form or as an acid addition salt. For the purposes of the present invention, apomorphine hydrochloride is used.

[0029] The compositions described in the Examples allow for the release and control of mucosal absorption of the apomorphine permitting the desired plasma levels at the concentration maximum to be achieved. The compositions afford other significant attributes as well. Apomorphine is an unstable chemical moiety in the presence of light, and oxygen. The formulation composition affords the chemical moiety unique stability as measured by continuous testing of the preparations. Further, hydroxypropylmethylcellulose in combination with microcrystalline cellulose and mannitol perform as a matrix where in the presence of saliva, swell and allow for the sufficiently controlled release of the apomorphine, thus controlling the plasma concentration of the drug. Further, these formulae can be flavored in addition to a variety of sweeteners to overcome the unpleasant taste and bitter after-taste of this drug. The purpose of the flavoring agents is two fold. First: the formulation flavored with a mild mint flavor affords to the desirability of the sublingual tablet (which can remain under the tongue for up to 10 minutes). Second: the use of mint type flavors can attenuate some

of the local emesis type receptors located in the oral/pharyngeal region of the patient. This is desirable because localized stimulation of the receptors by apomorphine can exacerbate the nausea associated with this drug.

[0030] Formulation stability and the stabilizing effect of the tablet matrix are extremely valuable for to the practice of this invention. Apomorphine hydrochloride is known to be unstable in the presence of air and light. Apomorphine rapidly oxidizes in a variety of quinone, diquinone compounds when this drug is exposed for relatively short periods of time to air and light. These diquinones so formed can and do dimerize producing highly conjugated compounds which appear in the product as visible color. Thus, not only is the potency of the apomorphine at risk, but the overall product elegance can be violated making the product unacceptable as a drug product.

[0031] To overcome this problem, the tablet matrix has been developed furnishing the apomorphine with significant stability. This is accomplished by first the composition of the tablet, and the means in which it is prepared. Significant to this invention is the process by which the ingredients are added to prepare the tablets. The procedure used in adding the components of the drug product represent a physical means of enveloping the drug substance with an appropriate barrier reducing the oxygen tension at the physical location of the drug substance contained. Upon compression of the formulation into the drug product, i.e., the sublingual tablet, drug substance is well protected from ambient oxygen affording this product shelf stability and elegance.

EXAMPLE 1: Direct Compression Composition

[0032] Compositions were mixed from dry ingredients and formed into tablets by the direct compression method. Compositions were prepared by weighing the amounts of the ingredients. Each ingredient was passed through an appropriate sized (30 mesh) screen. The apomorphine HCl, ascorbic acid, aspartame, Turquoise Lake, and the citric acid were placed into a blender and blended for 5 minutes. Hydroxypropyl methylcellulose (Methocel E4M, Premium), the water dispersible polymer, was added to the blender and mixing was continued for an additional 5 minutes. Microcrystalline cellulose (Avicel PH102) was then added to the blender and mixing was . continued for an additional 5 minutes. Next, the mannitol was added to the blender and mixed for an additional 5 minutes. Finally, the magnesium stearate was added to the blender and mixed for an additional 2 minutes to yield a final powder mix. The final powder mix was transferred to a suitable tableting machine equipped with the appropriate sized tooling and compressed into tablets.

[0033] Dissolution was measured using USP Type II apparatus (USP XXIII) stirred at 30 rpm. The dissolution medium was 700 ml of distilled water at 37 degrees Celsius. Apomorphine released into the medium was analyzed by high pressure liquid chromatography (HPLC). Dissolution kinetic (K_{diss}) constants were calculated assuming first-order release kinetics. The tablets prepared were compared against a commercial soluble apomorphine HCl tablet (Apomorphine HCl tablet 6mg, Lot # 1000AP, Anpro Products, Arcadia, CA.) for dissolution characterization. The results are presented in FIGURE 1.

EXAMPLE 2: Direct Compression Composition R

[0034] Composition R was prepared by weighing the amounts of the ingredients, listed in the Table below, mixing the ingredients and forming tablets by the direct compression method as described in Example 1. Dissolution of the tablets was measured as described in Example 1. The results are presented in FIGURE 1. The values of T_{90} obtained were in the range 35-45 minutes.

EXAMPLE 3: Direct Compression Composition S

[0035] Composition S was prepared by weighing the amounts of the ingredients, listed in the Table below, mixing the ingredients and forming tablets by the direct compression method as described in Example 1. Dissolution of the tablets was measured as described in Example 1. The results are presented in FIGURE 1. The values of T_{90} obtained were in the range 30-45 minutes.

Table :

Direct Compression Compositions		
Ingredient (mg/tablet)	R	S
Apomorphine HCl, USP	40.0	40.0
Ascorbic Acid, USP	7.5	8.4
Citric Acid, Anhydrous, NF	5.0	5.6
Microcrystalline Cellulose, NF (Avicel PH102)	57.0	39.2

Table : (continued)

Direct Compression Compositions		
Ingredient (mg/tablet)	R	S
Magnesium Stearate, NF	3.0	2.8
Hydroxypropyl methylcellulose (Methocel E4M Premium, NF)	12.5	8.4
Turquoise Lake	3.0	2.8
Aspartame, USP	2.5	2.8
Mannitol, USP, powder	19.5	30.0
TOTAL, mg/tablet	150.0	140.0

Claims

1. An apomorphine direct compression tablet suitable for sublingual or buccal administration, having a drug release time T_{90} value in the range of 30 to 45 minutes and suitable for treating psychogenic erectile dysfunction, comprising the following components (mg/tablet) and wherein each component passes through a 30 mesh screen in either composition R or composition S:

	Composition	
Ingredient (mg/tablet)	R	S
Apamorphine HCl USP	40.0	40.0
Ascorbic Acid, USP	7.5	8.4
Citric Acid, Anhydrous, NF	5.0	5.6
Microcrystalline Cellulose, NF (Avical PH102)	57.0	39.2
Magnesium Stearate, NF	3.0	2.8
Hydroxypropyl methylcellulose (Methocel E4M Premium, NF)	12.5	8.4
Turquoise Lake	3.0	2.8
Aspartame, USP	2.5	2.8
Mannitol, USP, powder	19.5	30.0
TOTAL, mg/tablet	150.0	140.0

Patentansprüche

1. Eine Apomorphin-direkte Kompressionstablette, geeignet für eine sublinguale oder bukale Verabreichung, die einen T_{90}-Wert der Arzneimittel-Freisetzungszeit von 30-45 Minuten aufweist und zum Behandeln von psychogener erektiler Funktionsstörung geeignet ist, umfassend die nachstehenden Bestandteile (mg/Tablette) und worin jeder Bestandteil ein 30-mesh-Sieb passiert, in entweder Zusammensetzung R oder Zusammensetzung S:

	Zusammensetzung	
Bestandteil (mg/Tablette)	R	S
Apomorphin HCl, USP	40,0	40,0
Ascorbinsäure, USP	7,5	8,4
Citronensäure, wasserfrei, NF	5,0	5,6
Mikrokristalline Cellulose, NF (Avical PH102)	57,0	39,2
Magnesiumstearat, NF	3,0	2,8
Hydroxypropylmethylcellulose (Methocel E4M Premium, NF)	12,5	8,4
Türkisfarbene Pigmentfarbe (Turquoise Lake)	3,0	2,8
Aspartam, USP	2,5	2,8
Mannitol, USP, Pulver	19,5	30,0
GESAMT, mg/Tablette	150,0	140,0

Revendications

1. Comprimé de compression directe d'apomorphine approprié pour administration sublinguale ou buccale, ayant une valeur T_{90} de durée de libération du médicament dans l'intervalle de 30 à 45 minutes et approprié pour le traitement du dysfonctionnement érectile psychogène, comprenant les composants suivants (mg/comprimé) et dans lequel chaque composant passe à travers un tamis de 30 mesh dans l'une ou l'autre des compositions R ou S:

	Composition	
Composant (mg/comprimé)	R	S
Apomorphine HCl, USP	40,0	40,0
Acide ascorbique, USP	7,5	8,4
Acide citrique, anhydre, NF	5,0	5,6
Cellulose microcristalline, NF (Avicel PH102)	57,0	39,2
Stéarate de magnésium, NF	3,0	2,8
Hydroxypropyl méthylcellulose (Methocel E4M Premium, NF)	12,5	8,4
Colorant turquoise	3,0	2,8
Aspartame, USP	2,5	2,8
Mannitol, USP, poudre	19,5	30,0
TOTAL, mg/comprimé	150,0	140,0

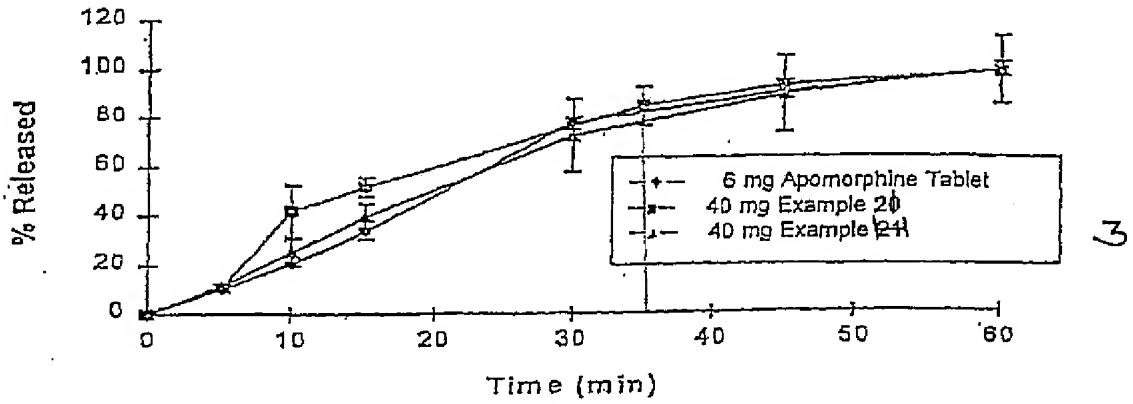

120
100
80
60
40
20
0
% Released
0
10
20
30
40
50
60
Time (min)
6 mg Apomorphine Tablet
40 mg Example 20
40 mg Example 21

FIG. 1